DETAILED ACTION

In view of the appeal brief filed on January 22, 2008, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/JD Schultz, PhD/

Supervisory Patent Examiner, Art Unit 1635.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on December 19, 2006 was unavailable to the examiner prior to the December 22, 2006 mailing date of the final office action. The submission is in compliance with the provisions of 37 CFR 1.97.

Accordingly, the information disclosure statement is being considered by the examiner and an initialed copy accompanies this action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75, 76, 78, 79 and 82-98 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use of double stranded RNAs of a length greater than 141 base pairs to inhibit GFP, Zf-T, Pax 6.1 and NKx 2-7 in zebrafish embryos, use of double stranded RNAs of a length greater than 201 base pairs to inhibit HirA in chick neural crest explants and use of double stranded RNAs of a length greater than 187 base pairs to inhibit GFP in NIH3T3 cells, does not reasonably provide enablement for use of double stranded RNAs targeted to any other foreign, endogenous or pathogen genes in all types of vertebrate cells. The specification further does not reasonably provide enablement for an *ex vivo* method that includes treatment of an explanted cell with dsRNA followed by implantation into an organism and does not reasonably provide enablement for using this *ex vivo* method to treat a disease or pathogen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

The nature of the invention and the breadth of the claims

The claims are directed to methods of *ex vivo* attenuation of gene expression in a vertebrate cell comprising explanting a cell from a vertebrate organism, supplying the cell with double stranded RNA, and implanting the cell into a vertebrate organism. The claims encompass methods of transplantation, including not only syngeneic, but also allogeneic and xenogeneic transplantation. In the embodiments of claims 96-98, the target gene is associated with a disease or pathogen. In other embodiments the target gene is endogenous, foreign, chromosomal or extrachromasomal; the function of the target gene may be unknown. The claims are further directed to a method that identifies a phenotypic change in the treated cell.

The amount of direction provided by the inventor and the existence of working examples

The specification teaches at page 2 that the present invention allows for attenuation of gene expression in a cell and teaches that inhibition of gene function is evidenced by a reduction or elimination of the activity associated with the protein encoded by the target gene. The specification further teaches at page 2 that the attenuation of gene expression is specific for the targeted gene. The specification contemplates a method of treating or preventing disease or infection in a mammal and teaches at page 4 that the methods of the invention can be used to target an endogenous gene or a pathogen gene for medical applications. The specification also states that the method could be used to treat disease or infection, providing general guidance at pages 15-16 of how the RNA would be delivered to the cell and that endogenous or pathogen genes can be targeted, but provides no specific guidance how to overcome the art recognized problems associated with use of transplanted cells.

The working examples of the specification describe the use of dsRNA to inhibit expression of several well characterized genes, including two reporter genes (GFP and Zf-T) in zebrafish embryos. Each of these examples uses long double stranded RNAs: GFP is targeted with dsRNA of 187 base pairs, Zf-T is targeted with dsRNA of 321 base pairs, Pax 6.1 is targeted with dsRNA of 298 base pairs and Nkx 2-7 is targeted with dsRNA of 141 base pairs. Further working examples describe the use of dsRNA of 201 base pairs targeted to HirA in explanted chick neural crest tissue and the use of dsRNA of 187 base pairs targeted to the reporter gene GFP in NIH3T3 cells. None of the working examples describe *ex vivo* treatment of a cell followed by implantation into any organism for any purpose.

The specification teaches that the instant invention provides a method of attenuating gene expression and states that this attenuation is specific for the targeted gene; however those in the art were aware that administration of dsRNA to vertebrate cells results in a non-specific response that leads to general suppression of protein synthesis and cell apoptosis. The working examples of the specification use long dsRNA that would be expected to produce this response. There is no disclosure in the specification regarding how to overcome the non-specific effects reported in the prior art when double stranded RNAs are added to vertebrate cells.

The state of the prior art, the level of ordinary skill in the art and the level of predictability in the art

The level of ordinary skill in the art is high, however there are several aspects of the invention that are unpredictable in view of the disclosure of the instant specification and the knowledge found in the prior art. These aspects include the limited applicability of the results observed in the specification's working examples to the broad scope of the claims, the unpredictability of RNA interference in vertebrate cells, the unpredictability of methods that use transplanted cells, and the unpredictability of using transplanted cells for the purpose of treating disease.

Most organisms exhibit an immune response (termed the PKR response) that results in non-specific translation arrest and is triggered by even small amounts of double stranded RNA. This response has precluded the use of dsRNA *in vivo* to specifically attenuate gene expression and the unpredictability of specifically attenuating

expression of a target gene in vertebrate cells by RNA interference (RNAi) is evident in both pre-filing and post-filing art, particularly with regard to avoidance of this response. This unpredictability extended for at least a year after the filing date.

The specification provides examples wherein RNA interference performed in cultured vertebrate cells specifically attenuates gene expression; however, for each system used, these examples aren't commensurate in scope with the claims. Because the cells used lack a full immune response the experimental results of the specification cannot be extrapolated to cells having this response.

One set of working examples describes experiments performed in zebrafish embryos. These experiments use dsRNAs ranging in size from 141-298 base pairs to target both reporter genes and endogenous genes and describe that the targeted gene is attenuated specifically. However, upon careful reading of the specification it becomes apparent that experiments in zebrafish embryos are not representative of the effect of dsRNA on vertebrate cells. The instant specification discloses at page 34, lines 15+ (emphasis added),

> "Immune system or interferon-α/β-mediated toxicity is very unlikely to play any role in generating the phenotypes we have observed. First, the phenotypes that we have generated can be observed in 24 hour embryos, **long before the zebrafish immune system has been established**. The thymus primordium appears in the zebrafish at approximately 54 hours, but does not enlarge significantly until 30 hours later. Rag1 and Rag2 expression cannot be detected until day 4, indicating a lack of mature T cells in the zebrafish until that time. Second, the amount of double-stranded RNA that was used to generate the phenotypes is much less than is necessary to cause this interferon-mediated cell toxicity."

Since, as applicants themselves have observed, the zebrafish embryos used in the working examples lack an immune system those of skill in the art would conclude that despite the positive results observed in the working examples of the specification,

the zebrafish embryo is not a suitable model for specific inhibition of gene expression using RNAi. The results observed in this system would not lead the skilled artisan to believe the RNAs used in the examples would avoid the PKR response in cells able to mount this response.

Another system used in the working examples is explanted chick neural crest tissue, an embryonic tissue. The thymus, an organ involved in the immune system, is derived from neural crest tissue (see Le Douarin et al.); therefore one of skill in the art would expect that this tissue is also unable to mount an immune response to dsRNA. Therefore, experiments performed in chick neural crest tissue do not provide results that can be extrapolated to the broad scope of cells embraced by the claims.

Another example in the specification describes targeting of the exogenous reporter gene GFP in NIH3T3 cells, but based on results with this cell line, which is derived from mouse embryo, it is likely that this cell lines does not exhibit the PKR response in the same fashion as adult cells. A hallmark of the PKR response is inhibition of protein production, but Epstein et al. (European Journal of Biochemistry 1981) teach that the NIH 3T3 cell line does not respond to some activities of interferon and in fact, addition of dsRNA to extracts of these cells has no effect on protein synthesis. Caplen et al. (Gene 2000, of record) teach that despite the existence of evidence of co-suppression (another term for RNAi), transfection of dsRNA into mouse NIH 3T3 cells transduced with a retrovirus expressing βgal induced no detectable decrease in gene expression (see pages 102-103). Caplen et al. further teach it is possible that gene, cell-type, or developmentally specific effects influence the balance

between specific and non-specific responses to dsRNA. Caplen et al. note that these possibilities would need to be taken into account when considering RNAi in mammalian cell systems.

The use of suitable models is critical in order to predictably extrapolate experimental results to other cell types, but the results observed in the examples are not broadly applicable to all vertebrate cells. While RNAi has been observed in other vertebrate embryo systems, those in the art question the general applicability of these results. Wianny et al. (Nature Cell Biology 2000, of record) reported that dsRNA can be used as a specific inhibitor of gene activity in the mouse oocyte (targeting c-mos) and preimplantation embryo (targeting E-cadherin or a GFP transgene) without causing a general translation arrest. However, the authors indicate (see page 73, under Discussion) that it is possible the early mouse embryo is incapable of the interferon response that would result in general translation arrest and that there may still be difficulties in using RNAi at later stages.

More than a year after the filing date of this application, the field of RNA interference determined that shorter dsRNA molecules of 21-23 nucleotides could avoid the PKR response in vertebrate cells and provide a more predictable inhibitory response. Elbashir et al., who first reported that short RNAs effectively inhibited expression, recognized the importance of avoiding the PKR response. Elbashir et al. state at page 494,

> "...it is known that dsRNA in the cytoplasm of mammalian cells can trigger profound physiological reactions that lead to the induction of interferon synthesis. In the interferon response, dsRNA> 30 bp binds and activates the protein kinase PKR and 2', 5'- oligoadenylate synthetase (2', 5' -AS)."

It was well known in the art that RNA of greater than 30 base pairs induces the PKR response; however, the working examples describe experiments using RNAs that are much longer; having a length of at least 141 base pairs. Applicants explicitly address at page 34 why the zebrafish embryo does not induce this response. The specification briefly contemplates at page 12 that the RNA used in the method can be as short as 25 base pairs but aside from the discussion at page 34 the specification provides no discussion of the PKR response, provides no discussion of how to avoid this response and provides no specific guidance regarding length of the RNA that would direct the skilled artisan to the use of shorter dsRNAs as a way to overcome the PKR response.

Thus, the art clearly suggests that administering dsRNA to vertebrate systems, either *in vitro* or *in vivo*, to attenuate target genes is not a reproducible or predictable art and that this unpredictability extended at least one year after the filing date of the instant application. The examples provided in the specification are not commensurate with the claims, which are directed to RNA interference performed in any vertebrate cells. The examples use long dsRNA, known to those in the art to induce the PKR response. The working examples appear to avoid this response because the cells used are embryonic and do not have the full immune system necessary to exhibit this response.

Claim 75 specifically recites that the cell treated with dsRNA is subsequently implanted into an organism. The claims embrace not only syngeneic transplantation, but also allogeneic and xenogeneic transplantation. Post-filing art teaches that such cell transplantation is unpredictable; an unpredictability exemplified in neuronal cell

transplants. Armstrong et al. (Neuroscience 2001) report at page 201, column 2, that histoincompatible allografts and neural xenografts are rejected within days or a few weeks with a vigor related to the degree of genetic disparity between donor and host, wherein the greater phylogenetic distance between donor and host, the more rapid and vigorous this rejection process. Loseva et al. (Brain Research 2001) observed that xenografts of embryonic chicken brain were rapidly rejected from rat brain. These references clearly demonstrate the incompatibility and ultimate rejection of xenografts between donor and host species.

The unpredictability of cell transplantation of neuronal cells is generally applicable to other cell types. With regard to a xenogeneic or allogeneic transplant, one major problem associated with these transplants is loss or rejection of the cell. Platt (Nature 1998) teaches at page 11, second column, that the loss or rejection stems from an immune response to the foreign cell. While one might use drugs to immunosuppress a host, the specification does not teach how to use such drugs in context of the instantly claimed methods of gene inhibition. In addition to this, Platt teaches at page 14 (in box 1), that a skilled artisan would need to know how to prevent infection of the host organism while the host's immune system is suppressed.

Gage (Nature 1998) teaches that while use of syngeneic cells may circumvent the problem with cell rejection, issues exist even with syngeneic transplants. Gage teaches that if long-term survival is required for gene therapy, the success of the graft appears to depend on the cell type, the site of implantation and the type or class of promoter used (page 19, first column). Alternatively, in the cases that require a cell to

integrate into a homotypic region and perform specific physiological roles, a skilled artisan would need to know the phenotype of the cell and the spatial location critical to its utility (e.g. a retinal cell transplant or a skin graft) (see page 19).

Thus, for reasons described above, a xenogeneic or allogeneic transplant of cells faces the problem of host rejection. The methods involved to reduce the chance of rejection would need to be empirically determined. Coupled with this, reducing rejection may involve methods of reducing infection in the host. This, too, would need to be empirically determined. In the case of syngeneic cells, a skilled artisan would need to be taught what kind of cells should be isolated, how to isolate said cells, and how to culture said cells. This would need to be empirically determined.

Claims 96-98 are additionally directed to treatment of disease by transplanting cells wherein the targeted gene associated with a disease or with a pathogen such as a virus or bacterium. While the specification contemplates at pages 15-16 that the disclosed methods can be performed *ex vivo* and can be used to treat disease, there is no specific guidance regarding how treatment is to be performed. The specification provides no working examples describing targeting of any disease or pathogen gene and provides no examples wherein a cell treated *ex vivo* is implanted into an organism for the purpose of treating any disease.

Coburn et al. (Journal of Antimicrobial Chemotherapy 2003, of record) point out that the major impediment to using RNA interference as a therapeutic is that gene expression is transient and the delivery methods used for RNAi are not effective for therapeutic purposes (see for example page 754, first column, last paragraph). Those

of skill in the art of RNA interference are optimistic about the potential of RNA interference as a therapeutic tool, but even with the advances made subsequent to the filing of the instant application, the field recognizes several years after the time of invention that therapeutic methods are not yet effective.

The quantity of experimentation needed to make the invention based on the content of the disclosure

At the time of filing, those of skill in the art were well aware of the non-specific PKR response induced by administration of dsRNA to vertebrate cells which leads to a general suppression of protein synthesis and cell apoptosis. Because the results of the experiments described in the working examples are not generally applicable to all vertebrate cells, one of ordinary skill in the art would not have believed the methods disclosed in the instant specification would produce sequence-specific inhibition of gene expression in vertebrate cells because the administered dsRNA would be expected to activate mechanisms including the PKR kinase and inhibit all gene expression. While those in the art have subsequently determined that dsRNAs of shorter length will provide specific inhibition of expression, the specification provides no specific guidance regarding the length or RNA to be used; merely contemplating that RNAs of 25-400 bases are useful. Therefore in order to perform the claimed invention throughout its full scope at the time of filing the skilled artisan would have had to perform trial and error experimentation to discover the length of RNAs that will provide specific attenuation of expression in all vertebrate cells.

Despite the general knowledge of the PKR response, the instant specification provides no specific guidance of how this response is to be overcome. Because the prior art teaches that administration of dsRNA to vertebrate systems is not a reproducible or predictable art, and the only experiments performed in specification were carried out in cells that appear to lack the PKR response, in order to practice the instantly claimed invention throughout its entire scope the skilled artisan would have to engage in undue, trial and error experimentation to determine which genes can be attenuated in zebrafish embryos, chick neural crest tissue explants and NIH 3T3 cells and this experimentation would have to be repeated for each type of cell in which the claimed method is to be performed in order to determine which genes can be attenuated using dsRNA without inducing the interferon response.

Additionally, based on the teachings of the prior art with regard to predictability of transplantation, particularly xenogeneic or allogeneic transplantation, once the skilled artisan has determined which genes can be attenuated in which types of vertebrate cells, additional undue trial and error experimentation would have to be performed to determine which of these vertebrate cells could be successfully transplanted into an organism while avoiding rejection of the transplant or infection of the host and persist long enough for an effect to be observed. For targeting of disease or pathogen genes, one of skill in the art would have to further experiment to determine what disease genes can be inhibited by transplanted cells in order to provide a therapeutic effect.

Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for the broad claims of introducing any

dsRNA for any target gene in any vertebrate cell followed by transplantation into an organism because the art of attenuating gene expression by introducing dsRNA into a cell or organism is neither routine nor predictable. Because one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation the claims are not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 75, 76, 78, 79, 82-91 and 93-98 are rejected under 35 U.S.C. 102(e) as being anticipated by Fire et al. (US 6,506,559).

The claims are directed to methods of *ex vivo* attenuation of gene expression in a vertebrate cell comprising explanting a cell from a vertebrate organism, supplying the cell with double stranded RNA and implanting the cell into a vertebrate organism. Specific embodiments recite that the cell is implanted in the same organism, the RNA is less than 200 bases, the RNA comprises at least 25 nucleotides complementary to the target and the RNA is supplied by expression from a DNA sequence or direct delivery.

In other embodiments the target gene is endogenous, foreign, chromosomal or extrachromasomal; the function of the target gene may be unknown or it may be associated with a disease or a pathogen such as a virus, bacterium, fungus or protozoan. The RNA may be comprised of a single, self-complementary strand or two strands that may be annealed in the presence of potassium chloride. The claims are also directed to a method that further comprises identifying a phenotypic change in the treated cell.

Fire et al. disclose a method of inhibiting gene expression using a double stranded RNA. At column 10, lines 12-14 the invention is disclosed as including methods performed in cells *ex vivo* (explanted cells) and subsequently implanted into an organism. At column 8 the method is disclosed as being performed in vertebrates. The genes targeted can be an endogenous gene or a transgene, which is a foreign gene, or can be from a pathogen (see column 6, lines 45-49). Fire et al. disclose at column 7, line 67-column 8 line 6 the limitations on hybridization conditions and length recited in the claims; the dsRNAs used in the disclosed examples were purified without phenol and chloroform. The dsRNA can be formed from 1 or 2 strands (see column 4, lines 41-46). The method of Fire et al. can be used to treat disease and the dsRNAs can be delivered via several different means (see column 9, lines 48-64).

Thus, Fire et al. disclose all the limitations of and anticipate claims 75, 76, 78, 79, 82-91 and 93-98.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 75, 76, 78, 79 and 82-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (of record) in view of Ekenberg et al. (of record).

The claims are directed to methods of *ex vivo* attenuation of gene expression in a vertebrate cell as described in the previous 102 rejection. Claim 92 recites that the RNA may be treated with RNase prior to delivery.

Fire et al. teach a method of inhibiting gene expression using double stranded RNA. Fire et al. teach that the method is general and target organisms include vertebrates such as fish. The genes targeted can be endogenous or a transgene, which is a foreign gene, or can be from a pathogen. The dsRNA can be formed from 1 or 2 strands, the method can be used to treat disease and the dsRNAs can be delivered via several different means. At column 9 Fire et al. teach that the RNA can be purified before administration to a cell. Fire et al. do not teach the use of RNase to purify the double stranded RNA prior to administration.

It was well known in the art at the time of invention that RNases such as RNase A and RNase T specifically degrade single stranded RNA in the presence of double stranded RNA. See, for example, Ekenberg et al., who describe a protocol for RNase

protection assays. This assay involves hybridization of an RNA probe and target, followed by removal of remaining single stranded RNA with an RNase specific for single stranded RNA in order to leave only RNA that is part of a double stranded structure.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use RNA purified by treatment with RNase in the method of inhibiting gene expression with double stranded RNAs taught by Fire et al. One of ordinary skill in the art would be motivated to purify the RNA used for inhibition of gene expression because Fire et al. specifically suggest use of purified RNA. One of ordinary skill would have been motivated to use an RNase specific for single stranded RNA for purification and would have had a reasonable expectation of success in doing so because the use of single-strand specific RNases in order to distinguish between single and double stranded RNA in RNase protection assays was well known.

Thus, the invention of claims 75, 76, 78, 79 and 82-98 would have been obvious, as a whole, at the time of invention.

Response to Arguments

Applicants' arguments traversing the rejection over Fire et al. focus on whether the reference provides an enabling disclosure. Applicants note that at the time of filing it was well known in the art that vertebrate cells possessed a non-specific response to double stranded RNA molecules that results in general translational arrest and induction of interferon synthesis. Applicants cite several references as evidence that the skilled

artisan had considerable difficulty using double stranded RNA in vertebrate cells due to this non-specific response and conclude that undue trial and error experimentation would be required to practice the claimed invention based on the disclosure of Fire et al. Applicants further argue that in contrast to Fire et al., which describes only examples performed in invertebrate organisms, the instant specification demonstrates successful attenuation of target gene expression of both endogenous genes and transgenes in vertebrate cells including vertebrate embryos, vertebrate explants, and vertebrate cell lines.

Applicants' arguments appear to be based on the proposition that Fire et al. is not an enabling reference because it does not exemplify use of dsRNA in vertebrate cells and does not describe how to overcome the well known PKR response while the instant specification demonstrates successful inhibition in vertebrate cells. This assumes that the working examples of the instant specification alone provide a sufficient disclosure to enable the claimed invention throughout its full scope.

While it is correct that Fire et al. do not exemplify use of dsRNA in vertebrate cells, the assumption that the examples in applicants' specification demonstrate a level of enablement different from the Fire et al. reference is incorrect for the reasons detailed above in the scope of enablement rejection. Specifically, the examples described in the instant specification were performed in embryos and embryonic tissues that either do not have an immune response or have an immune response likely to be compromised; therefore they do not provide a disclosure commensurate in scope with the instant claims. Because the instant specification does not describe attenuation of expression

that can be broadly applied to all vertebrate cells and does not provide guidance regarding how to overcome the PKR response the level of enablement of the instant application is considered equivalent to that of the Fire et al. reference.

Therefore to determine if the Fire et al. reference anticipates the instant claims, one need only consider whether the disclosure of Fire et al. reference provides all the teachings necessary to perform the invention of the instant claims.

With regard to where the method can be performed, Fire et al. disclose at column 8, lines 13-17, that suitable cells include plants, animals, protozoa, bacteria, viruses, or fungi and that the animal could be vertebrate or invertebrate. Fire et al. disclose at column 10, lines 11-14, that the method could be performed *ex vivo* followed by subsequent transplantation. With regard to the structure of RNAs used, Fire et al. disclose at column 7, line 67-column 8 line 6 that the RNA to be used comprises a duplex having a portion identical to the target gene and that the length of the portion identical to the gene may be at least 25, 50, 100, 200, 300 or 400 bases and recite the limitations on hybridization conditions; the dsRNAs used in the disclosed examples were purified without phenol and chloroform.

Applicants assert that, based on the teachings of the art, successful attenuation of expression in vertebrate cells involves considerable difficulty; however, the instant specification provides no specific guidance regarding how the applicants overcame the difficulties that, based on their own analysis of the art, they should have encountered. There is no indication in the instant specification that any experimentation was required to achieve this attenuation and in fact, the working examples of the instant specification

use RNAs having the structure and length disclosed in the Fire et al. reference in the cell type specifically disclosed by Fire et al. Therefore, based on the disclosure of the specification, one of skill in the art would recognize that this disclosure does not deviate from the blueprint provided by Fire et al. but merely uses the type of dsRNAs contemplated by Fire et al. in the types of cells specifically named by Fire et al. to provide the result disclosed by Fire et al.

Applicants additionally argue that even the inventor of the cited art expressed uncertainty whether the methods of attenuating gene expression by administration of double stranded RNA in nematodes was applicable to vertebrate cells, citing a non-patent literature publication by Fire. It is noted that this later comment by Fire has no bearing on the rejection of record, which is directed solely to the disclosure of the '559 patent.

Applicants additionally refer to recent court decisions as evidence that the disclosure of the Fire et al. reference is not enabling. Applicants refer to the decision in *Impax Laboratories, Inc. v. Aventis Pharmaceuticals, Inc.* after remand from the federal circuit, noting that the District Court of Delaware determined that mention of riluzole in a list of several compounds to treat a myriad of diseases did not anticipate claims to using riluzole to treat ALS. Applicants liken this broad disclosure to Fire et al. by noting that Fire et al. simply recites vertebrate cells as one of many cell types in which the target gene can reside. However, as noted above, the "many cell types" referred to by applicants are actually disclosed at column 8, lines 13-15 as including plants, animals, protozoa, bacteria, viruses, or fungi; one of ordinary skill immediately recognizes that

vertebrates are not part of a large laundry list, but as one of the two types of animal cells. The instant specification provides an almost identical definition of the cells useful in the claimed method at page 2, "The cell into which the dsRNA is introduced can be derived from or contained in any organism (e.g., plant, animal, protozoan, virus, bacterium, or fungus)."

Applicants refer to *Forest Laboratories Inc. v. Ivax Pharmaceuticals, Inc.*, noting that the federal circuit upheld a lower court's determination that a prior art reference did not anticipate a claim to the positive enantiomer of citalopram because the method of resolving the racemic mixture of citalopram was new and unpredictable at the time of the invention and would have required undue experimentation based on the knowledge of one of ordinary skill in the art at the time.

Applicants liken the fact pattern in *Forest Laboratories v. Ivax Pharmaceuticals*, whether a reference anticipates a compound if that compound cannot be easily obtained, to the instant case, asserting that Fire et al. merely mentions that the invention can be practiced in various cell types including vertebrate cells, but provides no direction on how to practice the invention in these various cell types. Applicants conclude this is analogous to the method of resolving racemates described in *Forest Laboratories*.

Applicants appear to believe the fact pattern in *Forest Laboratories* is relevant to the instant application because the Fire et al. reference provides no direction of how to perform their method in vertebrate cells. However, in *Forest Laboratories v. Ivax Pharmaceuticals*, the method of resolving racemates was new and unpredictable. In

contrast, the Fire et al. reference discloses the structure and size of the RNA to be used and the types of cells in which it can be used. As described above, the working examples in the instant application use RNAs having the structure and length disclosed in Fire et al. in cell types specifically disclosed in the reference. These examples demonstrate successful inhibition of expression and indicate that simply following the disclosure of Fire et al. can provide inhibition of gene expression in vertebrate cells.

Applicants assert that one of ordinary skill in the art would not have believed the methods disclosed in Fire et al. would produce sequence-specific inhibition of gene expression in vertebrate cells and conclude that because those who attempted to use similar methods failed to achieve the desired end result it was not within the ordinary skill in the art to attenuate gene expression of target genes in vertebrate cells despite the disclosure of Fire et al.

This argument is not persuasive because there is no indication in the instant specification that any experimentation was required to achieve the specific attenuation of expression disclosed in the working examples. Contrary to applicants' assertion, because the examples describe the use of RNAs having the structure and length disclosed by Fire et al. as useful for attenuating gene expression in vertebrate cells, one of skill in the art would conclude that for attenuation of the exemplified genes in the exemplified cell types, the Fire et al. disclose is enabling.

Applicants specifically traverse the rejection as it is applied to claim 78 by arguing that the limitations of this claim, that the double stranded RNA supplied to the vertebrate cell has a length of less than about 200 base pairs, is not explicitly or

inherently disclosed in the Fire et al. reference. Applicants assert that the specification of Fire et al. only describes the length of the nucleotide sequence identical to the target and notes that all the working examples use RNA of more than 200 base pairs. This argument is not persuasive because Fire et al. specifically state that the portion of the RNA identical to the target can be 25, 50 or 100 base pairs. Based on the disclosure that the dsRNA can be formed from two complementary strands, one of skill in the art would immediately recognize that duplexes formed from these embodiments would be double stranded RNAs of 50, 100 or 200 base pairs. The fact that Fire et al. do not exemplify use of dsRNAs of less than 200 base pairs is irrelevant; the disclosure of a reference is not limited to preferred or exemplified embodiments.

With regard to the obviousness rejection, applicants argue that the examiner has not made any remarks as to why the invention as a whole is obvious over either Fire et al. or Ekenberg et al. singly or in combination and concludes the examiner fails to set forth a *prima facie* case of obviousness for all claims except claim 92. Claims 75, 76, 78, 79, 82-91 and 93-98 are obvious because they have been rejected under 102(e) as anticipated by Fire et al., "anticipation is the epitome of obviousness" *(In re Skoner, et al.*, 186 USPQ 80 (C.C.P.A. 1975)).

Applicants further argue that one of ordinary skill in the art would not be motivated and have a reasonable expectation of success in modifying the methods disclosed in Fire et al., referring to the arguments presented with regard to the 102(e) rejection, that the skilled artisan would not have believed the administration of double

stranded RNA as disclosed by Fire et al. would have worked in vertebrate cells. This argument is not persuasive for the reasons set forth above.

Applicants additionally traverse the rejection as it applies to claim 92 by arguing that there is no disclosure in Fire et al. that purification can be enzymatic or that the purification encompasses separating double stranded RNA from single stranded RNA as would be the result of RNase treatment. Applicants further note that Fire et al. do not specifically recommend the use of purified RNA over non-purified RNA and the use of RNase would be incompatible with the specific working examples in Fire et al. Applicants further argue that treatment of a mixture of sense and antisense strands such as those used in the working examples of Fire et al. with RNases as disclosed by Ekenberg et al. could destroy the RNA molecules and render the invention unfit for its intended purpose. Applicants conclude that because this might happen, there is no motivation to make the proposed modification.

Applicants' arguments are not persuasive because an obviousness rejection does not require that Fire et al. specifically contemplate use of enzymatic purification or state that use of purified RNA is recommended. Additionally, the argument regarding the RNA used in the working examples of Fire et al. appears to be stating the treatment of unannealed RNA would be destroyed by treatment with the RNases taught by Ekenberg et al. This argument is not persuasive because Fire et al. specifically contemplate at column 7 that RNA duplex formation can be initiated outside the cell. Also, a prior art reference is not limited to the teachings of the exemplified or preferred embodiments.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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/Tracy Vivlemore/
Examiner
Art Unit 1635

TV
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